**IN THE UNITED STATES DISTRICT COURT**
**FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA**
**AT CHARLESTON**

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| **IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION** | **Master File No. 2:12-MD-02327**<br>**MDL 2327** |
| **THIS DOCUMENT RELATES TO:**<br><br>**WAVE 2 CASES LISTED ON MOTION EXHIBIT A** | **JOSEPH R. GOODWIN**<br>**U.S. DISTRICT JUDGE** |

**DEFENDANTS' RESPONSE IN OPPOSITION TO PLAINTIFFS' MOTION TO EXCLUDE THE OPINIONS AND TESTIMONY OF DEFENDANT ETHICON, INC. AND JOHNSON & JOHNSON'S EXPERT STEVEN MACLEAN, PH.D., P.E.**

Dr. Steven MacLean, Ph.D., P.E., is a polymer scientist and engineer who has actively practiced in his field for the past 20 years. *See* Resp. Ex. A, Expert Report of Dr. Steven MacLean ("MacLean Report"), at 10.[1] Plaintiffs raise five main grounds for excluding Dr. MacLean's opinions. Specifically, Plaintiffs argue that (1) Dr. MacLean is not qualified to offer biocompatibility or regulatory opinions; (2) his molecular weight opinions based on Ethicon's Seven-Year Dog Study are unreliable; (3) his cross-sectional schematic and opinions on theoretical total molecular weight are unreliable; (4) he is not qualified to offer pathology opinions; and (5) Dr. MacLean's experiments are unreliable. Plaintiffs' arguments are predicated on a misunderstanding of Dr. MacLean's opinions, and the Court should deny Plaintiffs' Motion.

[1] Dr. MacLean's Wave 2 Report is different from his Wave 1 General Report in that it incorporates the additional validation testing that Dr. MacLean submitted in a Supplemental Report in Wave 1. Plaintiffs adopted their Wave 1 motion to exclude Dr. MacLean's opinions. Notice of Adoption of Prior Daubert Motion of Steven MacLean, Ph.D. for Wave 2 [ECF 2422]. For these reasons, this Response refers to Dr. MacLean's Wave 2 Report, but Plaintiffs' Wave 1 motion to exclude Dr. MacLean's opinions and accompanying memorandum of law.

## BACKGROUND

In his Report, Dr. MacLean opines, *inter alia*, that Prolene is not subject to meaningful or quantifiable degradation *in vivo*. *See* Resp. Ex. A, MacLean Report at 94–96. Specifically, Dr. MacLean discusses the physical and chemical characteristics of polypropylene and Prolene, as well as the chemical effects of oxidation and sample preparation on those materials. *Id.* at 13–24. Dr. MacLean also sets forth his analysis of the relevant scientific literature and Ethicon tests on which he bases his opinion that Prolene does not meaningfully degrade in the human body. *Id.* at 27–40.

Dr. MacLean's Report also describes a simple control experiment designed to assess the validity of a hypothesis relied upon by Dr. Vladimir Iakovlev—Plaintiffs' pathology expert—as the basis of all his degradation opinions in this case, which he failed to test. Specifically, Dr. Iakovlev opines that Prolene oxidizes and degrades *in vivo* such that cracks or "nanocavities" in the degraded Prolene trap histological stains, forming a purple "bark" that Dr. Iakovlev can detect using light microscopy. *See* Resp. Ex. B, Iakovlev Expert Report at 8–9, 18–19 (discussing degradation theories). Although Dr. Iakovlev, who is not a polymer scientist, offers numerous polymer degradation opinions, all of them are dependent on his alleged visual detection of a degraded bark layer on the surface of Prolene.

Dr. Iakovlev has admitted that his hypothesis is capable of being tested by intentionally oxidizing pristine Prolene to determine whether the outer layer traps stain (*i.e.*, is visible as purple "bark"). *See* Resp. Ex. C, Iakovlev 9/11/15 Dep. 31:14–46:12. Although Dr. Iakovlev testified that he began conducting such a test in about September 2014 (*see id.* at 35:14–18), as of March 21, 2016 Dr. Iakovlev testified that he had chosen not to conduct the test at all, (*see* Resp. Ex. D, Iakovlev 3/21/16 *Stubblefield* Dep. 64:19–65:4).

Dr. MacLean, however, ran the control experiment Dr. Iakovlev failed to conduct. *See* Resp. Ex. A, MacLean Report at 53–71. Specifically, Dr. MacLean and a team of scientists working at his direction intentionally oxidized Prolene mesh samples using two distinct methods, and then used the same sample preparation and staining protocols used by Dr. Iakovlev to determine whether oxidized Prolene traps the stains. *See id.* at 55–56. It does not.

Dr. MacLean purposefully incorporated two distinct methods for intentionally oxidizing the Prolene samples. *Id.* First, to ensure that he had at least some oxidized samples of Prolene on which to conduct tests, Dr. MacLean subjected one batch of Prolene samples to ultraviolet radiation ("UV"), which is widely recognized in scientific literature to oxidize polypropylene, including Prolene. *Id.* Second, he exposed a separate batch of Prolene samples to a chemical oxidative medium utilized by Drs. Scott Guelcher and Russell Dunn, experts for plaintiffs in pelvic mesh litigation. *See id.*

Dr. MacLean conducted scanning electron microscopy ("SEM") on the samples, and found that while the UV-treated samples exhibited significant surface cracking, the chemically oxidized samples did not. *See id.* 57–59. Dr. MacLean's team then subjected Prolene samples treated using both oxidation methods for processing and staining according to Dr. Iakovlev's staining protocol. *Id.* at 59–61. Dr. MacLean's team also exposed rabbit skin tissue to this staining protocol as a positive control. *Id.* at 59–60. Dr. MacLean's analysis of these samples proved that even intentionally oxidized Prolene does not trap or otherwise hold histological stains. *Id.* at 61–63.[2] Thus, Dr. MacLean—using a valid and repeatable scientific methodology—showed that the lynchpin of Dr. Iakovlev's degradation theories is flawed and unreliable.[3]

[2] Dr. MacLean's investigation also shows that manipulation of a microscope's polarized lens when viewing Prolene can produce a bark along the surface of the fiber. *See id.* at 64–68 (explaining that slides for microscopy are prepared using a microtome to slice the mesh fibers, which causes variations in the thickness of the fibers in the slide which "can create edge artifacts under polarized light").

Dr. MacLean also explains in detail that the degradation opinions offered by Plaintiffs' experts Drs. Vladimir Iakovlev, Howard Jordi, Jimmy Mays, Duane Priddy, Scott Guelcher, and Uwe Klinge are not based on scientifically reliable evidence. *Id.* at 72–93.

Dr. MacLean then conducted additional experiments on intentionally oxidized Prolene in order to demonstrate that the results of the control experiment were repeatable, using five different Prolene devices. *See id.* at 64; *see also id.* at Appendix H ("Validation Report"). As before, Dr. MacLean intentionally oxidized Prolene using UV and chemical treatment methods. *Id.* at 1–3. Dr. MacLean's team also treated samples with fetal bovine serum, a protein-rich material that would hold a histological stain. *Id.* at 3. Rabbit skin tissue was again used as a positive control. *Id.* at 13; *see also* Mot. Ex. Z, Histion Laboratory Logs at 1 (listing rabbit skin controls in accession log).

The results of these experiments confirmed the findings of Dr. MacLean's first experiment. The samples that were treated in fetal bovine serum revealed a "bark" with blue granules similar to the Dr. Iakovlev's findings, even though the samples were not oxidized. Resp. Ex. A, Appendix H, Validation Report at 14–16. Again, the intentionally oxidized Prolene samples did not trap H&E stain. *Id.* at 17–20.

## ARGUMENT

### I. Dr. MacLean Is Qualified to Opine on Questions of Polymer Science.

Dr. MacLean is a polymer scientist and engineer who has actively practiced in his field for 20 years. *See* Resp. Ex. A, MacLean Report at 10. Dr. MacLean has a B.S. and M.E. in

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[3] Notably, Exponent's work based on this testing methodology has been published without revision in a peer-reviewed conference proceeding by the Society of Plastics Engineers. Mot. Ex. V, MacLean 4/18/16 Dep. 129:22-131:18; *see also* Resp. Ex. E, MacLean 4/18/16 Dep. Ex. 20, S. Benight, *et al.*, *Microscopy of Intentionally Oxidized Polypropylene-Based Mesh Material* (May 2016).

Mechanical Engineering, an M.S. in Material Science and Engineering, and a Ph.D. in Materials Science. *Id.* Dr. MacLean's work includes the development of novel polymer formulations to combat known modes of degradation, including oxidation. *Id.* He is a registered Professional Engineer in New York and Maryland, and a Senior Member of the Society of Plastics Engineers. *Id.* Through his education, training, and more than 15 years working at General Electric Plastics and SABIC Innovative Plastics, Dr. MacLean developed expertise in polymer analysis using various methods, including infrared spectroscopy, chromatography, and mass spectrometry, as well as optical, scanning electron microscopy, and transmission electron microscopy. *Id.* at 10–11.

Notably, Plaintiffs do not challenge Dr. MacLean's qualifications as a polymer scientist and engineer. Rather, Plaintiffs seek to exclude Dr. MacLean's supposed opinions on biocompatibility and regulatory issues. But Dr. MacLean has not disclosed and will not offer opinions regarding biocompatibility or regulatory issues in this litigation, a point Dr. MacLean has repeatedly explained at deposition. *See* Mot. Ex. B, MacLean 9/29/15 Dep. 40:23–41:6; 80:22–81:1; 162:12–14. The biocompatibility and regulatory "opinions" that Plaintiffs cite are merely background material in Dr. MacLean's report. *See* Resp. Ex. A, MacLean Report at 22–26. Because Dr. MacLean has not offered and will not offer opinions about biocompatibility or regulatory issues, Plaintiffs' Motion to exclude such opinions should be denied as moot.[4]

[4] Should Plaintiffs choose to cross-examine Dr. MacLean on industry accepted standards and procedures used to assess the biocompatibility of polymeric material, he has the relevant education, training, and experience to address those issues. As discussed in his report, Dr. MacLean was one of the technical architects that designed and implemented GE/SABIC's healthcare resin portfolio while serving as the Director of Global Agency Relations and Product Safety. *See* Resp. Ex. A, MacLean Report at 12 & Appx A. Part of Dr. MacLean's work in that capacity included ensuring that commercialized resin grades were assessed for biocompatibility using industry-accepted test methods. *Id.* at 12.

## II. Dr. Barbolt's Testimony Does Not Render Dr. MacLean's Opinions Unreliable.

Plaintiffs claim that "Ethicon's own scientists" agree with Plaintiffs' experts that "polypropylene, including Prolene, undergoes surface degradation after it is implanted in the body." Pls.' Mem. Supp. Mot. Exclude MacLean [ECF No. 2206] ("Pls.' Mem.") at 2–3. The only Ethicon scientist Plaintiffs cite is Dr. Thomas Barbolt, who testified during a 30(b)(6) deposition that surface degradation can occur. *Id.* at 3. A full reading of Dr. Barbolt's testimony shows that he referred to subjective observations of surface cracking, not the objective assessments necessary to establish whether Prolene meaningfully degraded *in vivo*:

> Q. Are you telling the ladies and gentlemen of the jury that when the outer surface of the polypropylene fibers crack and peel away from the surface, that that is not degradation?
> . . .
>
> [A.] I am telling listeners that the key endpoint of adverse effects of degradation are molecular weight and tensile strength, both quantitative measures, not subjective assessments of surface changes, but quantitative measures that hold great weight and suggest that there's no degradation to the Prolene fiber in terms that are significant.

Resp. Ex. F, Barbolt 1/8/14 Dep. 373:24–374:12; *see also id.* at 448:19–449:16.

In other words, Dr. Barbolt testified that certain Ethicon tests made subjective observations of surface cracking on some Prolene fibers, but there had been no quantitative testing to determine whether the Prolene meaningfully degraded. His testimony does not undermine the reliability of Dr. MacLean's opinions, which are based on peer-reviewed literature and objective testing of Prolene. Plaintiffs' argument lacks merit, and should be rejected by this Court.

## III. Dr. MacLean Properly Relied on Ethicon's Seven-Year Dog Study

Dr. MacLean opines that Prolene is not subject to meaningful degradation in the human body because, *inter alia*, Ethicon's Seven Year Dog Study ("Dog Study") has shown that Prolene

does not lose molecular weight *in vivo*. *See* Resp. Ex. A, MacLean Report at 46–52 (discussing the Dog Study and results). In relevant part, the Dog Study examined the effects of long-term implantation on 5-0 Prolene sutures by conducting gel permeation chromatography ("GPC") on the explanted sutures. *See* Mot. Ex. Q, Seven Year Data for Ten Year Prolene Study, at ETH.MESH.09888187 (Oct. 15, 1992). To determine if there had been a change in molecular weight, Ethicon compared the GPC data for the 5-0 Prolene sutures to 4-0 sutures, which were composed of the same Prolene resin with a diameter 50 microns larger than 5-0 sutures.[5] *Id.* at ETH.MESH.09888187–88. The study showed "no significant difference in molecular weight between the 4-0 Prolene control and the seven year explant." *Id.*

Plaintiffs claim that Dr. MacLean's opinions regarding degradation should be excluded because he bases these opinions on the Dog Study. *See* Pls.' Mem. at 7–10. Specifically, Plaintiffs assert that the GPC data from the Dog Study is unreliable since Ethicon compared the 5-0 Prolene suture explants to 4-0 sutures. *Id.* Plaintiffs' argument, however, is predicated on a misunderstanding of both the concept of molecular weight and Dr. MacLean's testimony.

Molecular weight is a measurement of the average size of the polymers in a particular substance. *See* Resp. Ex. A, MacLean Report at 15; *see also* Mot. Ex. B, MacLean 9/29/15 Dep. 237:9–22 (explaining that molecular weight is the average length of polymer chains in a substance). Because the measurement of molecular weight is focused on the size of polymers within a specimen, the physical dimensions of the specimen itself is irrelevant to the calculation.

Applying this basic principle of polymer science to the Prolene sutures, Dr. MacLean opined that there is no difference in the molecular weight of pristine 5-0 and 4-0 Prolene sutures

[5] Fifty microns is approximately half the thickness of a sheet of paper.

because "[i]t's the same resin formulation,[6] it's the same base polymer, [and] it has the same molecular weight coming out of the synthesis process[.]" *Id.* at 249:21–250:4; *see also id.* at 243:22–244:2. He testified that this is because the "baseline molecular weight" for Prolene is based on a "polymerization process that . . . happens well before processing" the Prolene resin into fibers of differing sizes. *Id.* at 239:19–240:20. Thus, Dr. MacLean explained that the *composition* of the substance—not its diameter—is the crucial factor in identifying a proper control for molecular weight analysis. *Id.* at 239:9–13; 247:18–248:3.

Having failed to identify any evidence that 5-0 Prolene sutures could have a different molecular weight than 4-0 Prolene sutures, Plaintiffs point to out-of-context excerpts from Dr. MacLean's deposition. *See* Pls.' Mem. at 8–9. But, again, there was no scientific basis for acquiring separate data to show that sutures composed of identical material have identical molecular weights. *See* Mot. Ex. B, MacLean 9/29/15 Dep. 251:13-21 ("And there is nothing wrong with using a 4-0 suture as a baseline here with the same exact resin formulation, same manufacturing process, to establish a baseline in the absence of a 5-0 [suture].").

Finally, the fact that the pristine Prolene sutures were manufactured in 1992 while the explanted sutures were from 1985 is immaterial. Prolene has remained virtually unchanged in formulation since its introduction, and the changes to additives that have been made over time did not affect Prolene's molecular weight. Resp. Ex. G, ETH.MESH.02268619–21. Accordingly, there was no methodological flaw in using the pristine 4-0 Prolene sutures manufactured in 1992 to determine the baseline molecular weight for the Seven-Year Dog Study.

[6] Ethicon's slight reduction of the amount of an antioxidant in Prolene would "not hav[e] any bearing on the molecular weight synthesis process," because "[t]hose are mutually exclusive" and there is "no interaction between those two things." *See* Mot. Ex. B, MacLean 9/29/15 Dep. 251:24-252:13.

## IV. Dr. MacLean's Cross-Sectional Schematic and Molecular Weight Calculations Are Based on Sound Scientific Principles.

Plaintiffs claim that Dr. MacLean's cross-sectional schematic and calculations of molecular weight derived from the data generated by Plaintiffs' experts are unreliable. *See* Pls.' Mem. at 10–11. Plaintiffs' arguments are nothing but an attempt to complicate a clear-cut issue.

Dr. MacLean performed a simple scientific analysis using two data sets ***generated by Plaintiffs' own experts***, namely molecular weight values derived from Dr. Jordi's nano-thermal analyses and "crust" thickness values reportedly measured by Dr. Iakovlev. *See* Resp. Ex. A, MacLean Report at 80–81. Applying the rule of mixtures—a fundamental concept in polymer science—Dr. MacLean used Dr. Jordi's and Dr. Iakovlev's measurements to opine that a bulk analysis would have been able to detect any changes in molecular weight due to surface degradation. Mot. Ex. B, MacLean 9/29/15 Dep. 276:23–277:12; *see also* Resp. Ex. H, Sperling, *Polymeric Multicomponent Materials: An Introduction* (1997) at 51–54 (describing rule of mixtures for polymers).

Plaintiffs' arguments that Dr. MacLean's analysis is unreliable are based on a faulty understanding of their own experts' work. For instance, Dr. MacLean acquired the data regarding crack depth from a paper by Drs. Iakovlev and Guelcher in which they measured the depth of the "bark" layer as 3 or 4 microns for most of his samples, with one sample with a crack depth of 5 microns. Mot. Ex. Y, Iakovlev, *et al.*, *Degradation of polypropylene in vivo: A microscopic analysis of meshes explanted from patients,* Soc. Biomat. (July 30, 2015) at 9. Thus, despite Plaintiffs' suggestions to the contrary, Dr. MacLean did not simply fabricate an "assume[d]" crack depth, but instead used the depths reported by Plaintiffs' own experts.

Similarly, Dr. Jordi did not find a ***drop*** in molecular weight of 4,500, as Plaintiffs contend. Pls.' Mem. at 10. Rather, Dr. Jordi's thermal analysis data corresponds to a molecular

weight ***value*** of 4,500. *See* Resp. Ex. A, MacLean Report at 80. Again, Dr. MacLean gleaned this data directly from Dr. Jordi's findings.

Thus, Dr. MacLean used a valid scientific approach based on Plaintiffs' experts' data to reliably demonstrate that if the observed "crust" layer in the Dog Study was degraded Prolene, the associated degree of degradation (*i.e.*, losses in molecular weight) could be quantified by conventional molecular-weight techniques. *See id.* Given that Dr. MacLean performed simple calculations using the data originating from Plaintiffs' experts, Plaintiffs' suggestion that Dr. MacLean's work constitutes "math-magic" is disingenuous at best.

**V. Dr. MacLean Is Not Offering Pathology Opinions.**

Plaintiffs argue that "Dr. MacLean offers numerous pathology opinions throughout the MacLean Report and MacLean Supplemental Report which he is unqualified to offer." Pls.' Mem. at 11. Plaintiffs identify the following as "pathology opinions" that Dr. MacLean offers: "1) artifacts in microtome processing; 2) opinions concerning Hematoxylin and Eosin (H&E) staining; and 3) opinions concerning artifacts related to histology and polarized light microscopy imaging." *Id.* at 12. But none of Dr. MacLean's opinions address questions of pathology.

Pathology is the study of the causes and effects of disease. *See, e.g.*, "Pathology," *Black's Law Dictionary* (10th ed. 2014) ("The branch of medical study that examines the origins, symptoms, and nature of diseases."). Anatomical pathology—Dr. Iakovlev's specialty—is the study of disease through examination of human tissue. *See, e.g.*, *Engelstad v. Va. Mun. Hosp.*, 718 F.2d 262, 263 (8th Cir. 1983) ("Anatomical pathology concerns the laboratory study and analysis of tissue disease, and the structural and functional changes caused by tissue disease."). None of Dr. MacLean's opinions address disease or the study of human tissue.

Plaintiffs misconstrue the term "pathology" as synonymous with "microtoming, microscopy, and staining." While a pathologist may use microtoming, microscopy, and staining

in their analyses, the application of these tools is not limited to pathologists. Indeed, microtoming, polymer-stain interactions, and polarized-light microscopy are general science concepts used in various fields of medicine and science, including polymer science. Dr. MacLean is more than qualified to develop and execute scientific experiments investigating the chemical and physical interactions between a fluid (such as H&E stains) and a polymeric material (such as Prolene), because such analysis is a basic aspect of polymer science.

Dr. MacLean is also well-equipped to determine whether H&E, or any other fluid, chemically or physically stains a polymer. Throughout his career, Dr. MacLean has routinely used microtoming and polarized light microscopy—tools used by polymer scientists for decades. *See* Resp. Ex. A, MacLean Report at 64 (citing literature); *id.* at 67–68 (citing literature).

Plaintiffs attempt to bolster Dr. Iakovlev's methods by pointing to an internal Ethicon test from the 1980s in which Ethicon scientists used a 1% aqueous Phloxine solution to stain the cracked crust layer of explanted sutures. *See* Pls.' Mem. at 13–14. But Plaintiffs appear to be oblivious of the fact that Dr. MacLean's opinions apply with equal force to the Ethicon test because the investigators did not run a control experiment to determine whether the allegedly oxidized Prolene could trap the Phloxine solution.

The conclusions from a single 32-year-old internal Ethicon test that failed to determine the validity of its own methodology cannot be said to undermine the reliability of Dr. MacLean's opinions. The Court should reject Plaintiffs' baseless arguments to the contrary.

## VI. Dr. MacLean's Experiments Are Reliable.

Neither Dr. Iakovlev nor any of Plaintiffs' other experts have ever run the control test necessary to validate Dr. Iakovlev's theory. Indeed, although Dr. MacLean first disclosed his

control experiment to Plaintiffs in September 2015, Plaintiffs continue to be unable to identify any scientific testing or literature contradicting Dr. MacLean's work.

Instead, Plaintiffs seek to distract the Court from Dr. MacLean's results by arguing that his experiments on Prolene were unreliable or irrelevant. Specifically, they claim that (1) the experiments did not replicate *in vivo* conditions; (2) Dr. MacLean did not adhere to Dr. Iakovlev's protocol; and (3) Dr. MacLean or Histion—the laboratory that prepared the samples—"manipulated the results through selection bias." Pls.' Mem. at 14–20. Plaintiffs misunderstand Dr. MacLean's opinions, and their arguments are without merit.

### A. Dr. MacLean's Control Experiments Were Not Intended to Replicate *In Vivo* Conditions and Lack of Replication Does Not Make Them Unreliable.

In arguing that Dr. MacLean's experiments are unreliable because they do not replicate *in vivo* conditions, Plaintiffs fundamentally misunderstand Dr. MacLean's opinions. Dr. MacLean's experiments were not intended to determine whether Prolene is subject to oxidative degradation under *in vivo* conditions. Rather, the purpose of Dr. MacLean's experiments was to assess the more basic question of whether oxidized Prolene is capable of trapping H&E stain, as this is the foundational predicate of Dr. Iakovlev's "bark" theory. *See* Resp. Ex. A, MacLean Report at 53; Appendix H, Validation Report at 1–2. The scientific method demands such control experiments because there are no authoritative polymer characterization treatises or peer-reviewed literature which support Dr. Iakovlev's notion that the use of H&E stain confirms degradation of a polymeric material.[7]

[7] Dr. Iakovlev's own words demonstrate that no publications, other than his own, advance the theory that degraded Prolene traps stain such that it is observable via light microscopy. *See* Mot. Ex. Y, V. Iakovlev, *et al.*, *Degradation of Polypropylene* In Vivo: *A Microscopic Analysis of Meshes Explanted From Patients*, J. Biomed. Mater. Res. Part B at 7 (2015) ("[W]e found no description of these findings in published literature after a search through online and printed sources."); Resp. Ex. I, V. Iakovlev 12/17/14 *In re Bos. Sci.* Dep. 194:4–6 ("I'm the first one who is describing light microscopy features of

In arguing that Dr. MacLean's experiments should have been conducted under *in vivo* conditions, Plaintiffs appear to misunderstand the purpose of a control. A control functions to isolate the variable being tested in an experiment. *See, e.g.*, "Control," *A Dictionary of Science* (2005); "Control Experiment," *Collins Dictionary*, http://www.collinsdictionary.com/dictionary/english/control-experiment ("An experiment designed to check or correct the results of another experiment by removing the variable or variables operating in that other experiment. The comparison obtained is an indication or measurement of the effect of the variables concerned."). Without running a control, an investigator cannot rule out the possibility that the results of a test were caused by the presence of other variables. This is a basic tenet of science.

The foundational predicate of Dr. Iakovlev's diagnostic technique is that oxidized Prolene traps or holds H&E stain such that the oxidized outer layer is visible using light microscopy. Thus, if oxidized Prolene does not trap H&E stain, Dr. Iakovlev cannot detect the "bark" layer under his microscope. For this reason, the key methodological variable is whether or not oxidized Prolene can trap H&E stain. In other words, Dr. Iakovlev's theory is independent of *in vivo* conditions and solely dependent on the presence of (i) oxidized Prolene, and (ii) H&E stain. Only by isolating these specific factors is it possible to determine that the "bark" layer is H&E stain trapped in the oxidized outer layer of a Prolene fiber, and not the product of confounding factors (*e.g.*, the sample preparation process, proteins, lipids). These are the precise factors Dr. MacLean isolated in his control experiments.

In arguing that Dr. MacLean should have conducted his experiments under *in vivo* conditions, Plaintiffs advocate re-introducing the very same variables that the scientific method demands be excluded in order to conclude that the "bark" layer is composed of oxidized Prolene

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polypropylene degradation."); *id.* at 239:15–240:2 (admitting that his own article is the only published paper reporting that degraded polypropylene traps histological dyes).

in which H&E stain has been trapped. Indeed, Plaintiffs are essentially arguing that Dr. MacLean should have re-run Dr. Iakovlev's analysis. Plaintiffs' argument simply misses the point of Dr. MacLean's experiments and ignores the scientific method.[8]

Plaintiffs also claim Dr. MacLean's use of UV radiation is unreliable because it does not duplicate the *in vivo* degradation process. Pls.' Mem. at 15. Plaintiffs' assertion directly contradicts their own experts' long-standing position that the ***only*** criteria needed to confirm *in vivo* oxidative degradation are (i) carbonyl functionality in the 1650–1740 $cm^{-1}$ range of the IR spectrum, and (ii) visual signs of cracking. *See, e.g.*, Resp. Ex. K, Jordi 2/1/16 Report at 11, 14–15 (Plaintiffs' polymer expert opining that tests confirmed degradation based on cracking and presence of bands at 1650 and 1740 $cm^{-1}$). Plaintiffs do not identify any scientific authority to the contrary.[9]

In his experiments, Dr. MacLean used generally accepted and repeatable methods to confirm that the UV-irradiated specimens satisfied both of the criteria that polymer scientists—including Plaintiffs' experts—have identified as necessary to confirm oxidation. Specifically, Dr. MacLean used SEM to confirm surface cracking, and FTIR to confirm the presence of carbonyl

[8] Dr. MacLean never claimed that the methods employed in his experiments were meant to replicate the conditions to which implanted meshes are exposed. Any assertion to the contrary is a gross mischaracterization of Dr. MacLean's opinions and testimony. Although Dr. MacLean used a chemical oxidation method from a paper by Dr. Guelcher which states that the "oxidative medium . . . recapitulates the microenvironment between an adherent macrophage and the [polypropylene] surface," (Resp. Ex. J, S.A. Guelcher & R.F. Dunn, "Oxidative Degradation of Polypropylene Pelvic Mesh *In Vitro*," 26 Int'l Urogyn. J. S55, S56 (2015)), Dr. MacLean made no such assertion.

[9] Plaintiffs' attempt to support their argument by pointing to a study by Clave cannot withstand scrutiny. Pls' Mem. at 15.As an initial matter, Plaintiffs not only ignore the fact that Dr. MacLean conducted control experiments, but they fail to recognize that the presence of numerous confounding factors in the human body is the precise reason a control experiment is necessary. Moreover, Plaintiffs ignore the fact that the study clearly states that the language quoted by Plaintiffs is merely a "hypothesis" that is not tested in the study. Mot. Ex. H, Clave, *et al. Polypropylene as a Reinforcement in Pelvic Surgery is Not Inert*, 21 Int. Urogynecol. J. 261, 267 (2010). Finally, the Clave study simply does not address UV radiation, much less state that it is an inappropriate mechanism for a control experiment.

groups at 1650–1740 $cm^{-1}$. Resp. Ex. A, Appendix H, Validation Report at 6, 8–10, 12. Tellingly, Plaintiffs fail to even mention Dr. MacLean's methods or observations on this point.

Because the same conditions that Dr. Iakovlev claims are required for H&E to become physically entrapped were present in Dr. MacLean's UV-irradiated specimens, Plaintiffs' attempt to distinguish the UV-irradiated specimens rings hollow.

The purpose of Dr. MacLean's experiments was to purposefully oxidize samples of Prolene and see if these samples trapped H&E stain, as Dr. Iakovlev claims. Dr. MacLean's experiments accomplished this goal through a reliable and repeatable methodology. Plaintiffs' assertion that Dr. MacLean's control experiment should have been conducted under *in vivo* conditions has no basis in science, and should be rejected by this Court.[10]

**B. Dr. MacLean's Experiments Adhered to Standard Staining Protocols Commonly Used Among Pathology Labs, Including Dr. Iakovlev's.**

Plaintiffs claim that Dr. MacLean's experiments are unreliable because he did not follow the same staining protocol used by Dr. Iakovlev. *See* Pls.' Mem. at 16–18. Plaintiffs' criticism is twofold: (1) that Dr. MacLean did not follow the exact same H&E staining protocol as Dr. Iakovlev, and (2) that Dr. MacLean did not perform other types of staining in his analysis. *See id.*

Nowhere in any of Dr. Iakovlev's expert reports or deposition testimony does he clearly define the staining protocol he used for Ethicon meshes in this litigation. In fact, in many cases, Dr. Iakovlev found "bark" in slides that were stained before he received them, with no indication of the staining protocol used. *See, e.g.*, Resp. Ex. L, Iakovlev (*Hooper*) Report at 11–12 (opining

[10] Plaintiffs miss the mark in attempting to equate Dr. MacLean's opinions with Dr. Barker's opinions that this Court excluded in *Sanchez*. Pls. Mem. at 16 (citing *Sanchez v. Bos. Sci. Corp.*, No. 2:12-cv-05762, 2014 WL 4851989 at *9 (S.D. W. Va. Sept. 29, 2014), *reconsideration denied by Sanches v. Bos. Sci. Corp.*, No. 2:12-cv-05762, 2014 WL 4851989 (S.D. W. Va. Oct. 17, 2014). This Court excluded Dr. Barker because, *inter alia*, he sought to offer opinions regarding the *in vivo* mechanical performance of the mesh products at issue without replicating *in vivo* conditions. *Id.* at **6–9. As discussed above, Dr. MacLean's control experiments were not intended to address *in vivo* conditions.

that H&E-stained slides prepared by explant facility showed degradation layer). Because Dr. Iakovlev failed to disclose his staining protocol in this litigation, Dr. MacLean relied on the protocol Dr. Iakovlev identified and testified about in *Bellew v. Ethicon*, which listed a series of chemical treatment steps and corresponding stain and rinse times for each step. *See* Resp. Ex. M, *Bellew v. Ethicon, Inc.*, No. 2:13-cv-22473 (S.D. W. Va.), Trial Exhibit DX10495 ("St. Michael's Staining Protocol").

Plaintiffs attempt to mask the absence of a disclosed protocol by referencing a recent journal article authored by Dr. Iakovlev. *See* Pls.' Mem. at 16–17; Mot. Ex. Y, Iakovlev, *et al.*, *Degradation of polypropylene in vivo: A microscopic analysis of meshes explanted from patients*, Soc. Biomat. (July 30, 2015). Since no such citation exists in any of Dr. Iakovlev's case-specific reports, Plaintiffs are taking the curious position that Dr. MacLean should have *assumed* that Dr. Iakovlev followed a protocol that he had not disclosed in litigation.

More importantly, Dr. Iakovlev recently testified that his staining protocols are the same standard protocols used in "all labs in North America," and that the specimen processing he used is "done the same way anywhere in the world." Resp. Ex. N, Iakovlev 4/19/16 (*Ramirez*) Dep. 234:4–17. Thus, Dr. Iakovlev's own words demonstrate that Histion, a reputable FDA-compliant histology lab with decades of staining experience, Mot. Ex. B, MacLean 9/29/15 Dep. 292:5–10, produced slides subject to the same staining processes as Dr. Iakovlev's slides.

Plaintiffs also argue that the protocol followed by Dr. MacLean is distinguishable because his samples "were oriented on vertical trays when they were stained rather than horizontal trays that Dr. Iakovlev's protocol required." Pls.' Mem. at 17. Tellingly, Plaintiffs fail to identify any scientific support for their assumption that staining slides on a vertical tray produces slides that are scientifically distinct from slides stained on a horizontal tray.

Furthermore, Plaintiffs ignore the generally accepted scientific fact that H&E stain works by ionic bonding, meaning the positively charged hematoxylin bonds with negatively charged substances, and negatively charged eosin bonds with positively charged substances.[11] The charge of the stains and a specimen is the same regardless as to the orientation of the slide. Plaintiffs' arguments are purely speculative and in conflict with widely known scientific principles.[12]

Finally, Plaintiffs' assertion that Dr. MacLean's experiments are unreliable because he did not apply trichrome stain like Dr. Iakovlev is a red herring. Pls.' Mem. at 17. Once again, Plaintiffs fail to grasp the fact that Dr. MacLean's control experiments were designed to answer the question of whether oxidized Prolene traps ***H&E*** stain. Moreover, this issue is irrelevant because Dr. Iakovlev's case-specific reports for Wave 2 cases do not discuss trichrome staining.

None of Plaintiffs' attempts to distance Dr. MacLean's protocol from Dr. Iakovlev's withstand scrutiny, and the Court should deny Plaintiffs' Motion on that basis.

**C. Dr. MacLean and Histion Did Not Manipulate Experimental Results.**

Plaintiffs point to several perceived flaws in Histion's experimental setup that they believe show selection bias. Specifically, Plaintiffs claim that (1) Histion rejected samples due to "overstaining" because "Histion and/or Dr. MacLean did not like these results," and (2) Histion materially deviated from its staining protocols for specimens that had failed quality control. Pls.' Mem. at 19. Plaintiffs' arguments have no basis in science or fact.

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[11] *See, e.g.*, Resp. Ex. O, D. Cook, *Cellular Pathology*, at 68 (2006) ("Eosin is an example of an anionic dye and is attracted to protein groups that are positively charged (cations) such as amino groups."); Resp. Ex. P, Suvarna, et al., *Bancroft's Theory and Practice of Histological Techniques* (7th ed.) ("*Bancroft's Theory and Practice*"), at 161 ("With the traditional acid dye-basic dye pairs (H&E, Papanicolaou, and Romanowsky) the negatively charged acid dyes have high affinities for tissue structures carrying cationic charges [but] low affinities for structures carrying negative charges . . . with the opposite being the case for basic dyes.").

[12] Dr. MacLean also used charged slides and employed manual staining, which is consistent with Dr. Iakovlev's purported protocol. *See* Mot. Ex. V, MacLean 4/18/16 Dep. 62:1–8 (testifying that manual staining was used for experiments); *id.* at 77:24–78:1 (testifying that stained slides were charged).

Plaintiffs argue that because Histion rejected certain paraffin-embedded samples due to "overstaining," Histion must have discarded samples where the Prolene fibers had actually retained stains. Pls.' Mem. at 19. As an initial matter, Plaintiffs fail to support any of their arguments with scientific literature. Instead, Plaintiffs advance arguments conceived by counsel and unfounded in science with the aim of clouding a straightforward issue.

Plaintiffs' assertions demonstrate a misunderstanding of Histion's quality control procedures. Histion is a GLP-compliant lab that routinely performs comprehensive studies on projects that will be reviewed by the FDA and other regulatory bodies. *See* Resp. Ex. Q, Smith Aff. at ¶ 4. Histion has institutionalized a rigorous quality control process, and is obligated to apply that process to all of its studies, regardless of project scope and specimen type. *Id.* at ¶¶ 4–5, 11. The scientific community recognizes that quality control is a fundamental component of preparing slides for analysis. *See, e.g.*, Resp. Ex. P, *Bancroft's Theory and Practice*, at 6.

Pursuant to its standard operating procedures, Histion followed a quality control procedure that required the technician to determine the effectiveness and quality of the staining for each batch of slides by assessing a positive control consisting of rabbit skin tissue. *See* Resp. Ex. Q, Smith Aff. at ¶¶ 5–6. In the event the rabbit tissue control failed quality control, Histion's procedure required the technician to reject the entire batch of specimens and prepare a new batch of specimens, modifying the staining protocol as necessary to ensure proper staining. *Id.* This is precisely what happened for two batches of specimens at issue in Dr. MacLean's experiments.

The Histion technician rejected one batch of resin-embedded specimens because the resin surrounding the rabbit tissue control stained "too dark" for appropriate evaluation because there was an excessive overlap in the intensity of the stain between the rabbit tissue and the slide background. *Id.* at ¶ 8. Similarly, the technician rejected one batch of paraffin-embedded samples

due to "overstaining," because there was insufficient contrast between the rabbit tissue control and the slide background. *Id.* at ¶ 9. In both instances, the technician rejected the entire batch of specimens based solely on the control, and not the slides containing Prolene. *Id.* at ¶¶ 8–9. Variability is an inherent part of staining slides, and "overstaining" is a well-known issue in slide preparation. *Id.* at ¶ 5. Contrary to Plaintiffs unsupported suggestions of impropriety, Histion's rejection of these batches demonstrates that it rigorously applied its quality control procedures.

With respect to the staining of subsequent samples, Plaintiffs cite two specific deviations that they claim prevented the Prolene fibers from holding stain. First, Plaintiffs attempt to distinguish Histion's preparation of the paraffin-embedded samples because it performed an additional water rinse and alcohol treatment step. Pls.' Mem. at 19. But Plaintiffs point to the necessary adjustments Histion made to the staining protocol pursuant to its quality control procedures to achieve the proper degree of staining on the rabbit tissue control. *See* Resp. Ex. Q, Smith Aff. at ¶¶ 6, 9. Moreover, Plaintiffs' argument ignores the fact that Dr. Iakovlev's own staining protocol incorporates three alcohol washes and two xylene washes after application of Eosin. *See* Resp. Ex. M, St. Michael's Staining Protocol. Thus, Plaintiffs' suggestion that Histion's additional water rinse and alcohol treatment "likely washed away the stain" is nonsensical and notably unsupported by scientific literature.

Second, Plaintiffs claim that the resin-embedded samples did not undergo an initial treatment with 100% alcohol, which meant that resin on the samples remained and prevented the stain from reaching the fibers. Pls.' Mem. at 19–20. Again, Histion's decision to forgo the initial alcohol step was based on their quality control process. *See* Resp. Ex. Q, Smith Aff. at ¶¶ 5–6, 8. Based on his professional judgment, training, and experience, the technician decided to eliminate the initial alcohol step because the resin surrounding the rabbit tissue control was stained too

dark in the initial batch. *Id.* at ¶ 8. Not only did this minor adjustment to the protocol remedy the problem, it would not have influenced Prolene's ability to react chemically with the H&E because alcohol is used to dehydrate specimens *with tissue*, not remove the resin as Plaintiffs suggest.[13] Plaintiffs' arguments are not grounded in science or fact, and should be rejected.

Ultimately, these alleged protocol deviations are meaningless. Minor fine-tuning to protocols is both common and expected in order to optimize histological staining. *See* Resp. Ex. Q, Smith Aff. at ¶ 5; Resp. Ex. P, *Bancroft's Theory and Practice*, at 440 ("Staining protocol development generally consists of trial and error, making sequential alterations in order to achieve optimal signal-to-noise ratio."). With respect to all specimens, Histion stained rabbit skin tissue as a positive control. After undergoing the same staining protocol as the Prolene specimens, the rabbit tissue controls showed that the staining was effective for both the paraffin-embedded and resin-embedded samples. *See* Resp. Ex. A, Appendix H, Validation Report at 13. Accordingly, any supposed deviations in Histion's staining protocols do not affect the reliability of Dr. MacLean's opinions based on the control experiments.

[13] *See, e.g.*, Resp. Ex. P, *Bancroft's Theory and Practice*, at 173 (discussing use of alcohols to dehydrate specimen); Mot. Ex. V, MacLean 4/18/16 Dep. 54:2–23 (discussing purpose of alcohol in specimen processing).

Respectfully submitted,

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**IN THE UNITED STATES DISTRICT COURT**
**FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA**
**AT CHARLESTON**

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| **IN RE ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION** | **Master File No. 2:12-MD-02327**<br>**MDL 2327** |
| **THIS DOCUMENT RELATES TO:**<br><br>**WAVE 2 CASES LISTED ON MOTION EXHIBIT A** | **JOSEPH R. GOODWIN**<br>**U.S. DISTRICT JUDGE** |

## CERTIFICATE OF SERVICE

I hereby certify that on August 8, 2016, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notification of such filing to CM/ECF participants registered to receive service in this MDL.

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